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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,641	03/01/2002	Paul Barth Conrad	STRATA-06663	3731

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EXAMINER

DAVIS, RUTH A

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 01/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/087,641	Applicant(s) CONRAD ET AL.	
	Examiner Ruth A. Davis	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 October 2003.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
 a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's amendment and response has been received and entered into the case. It is noted that on the bottom of page 5 of the amendment, it states that claims 11 – 13, 17, 68 and 29 – 33 are canceled. However, this does not appear consistent with the claims listing or remainder of the response. Therefore, this statement has been treated as an error; the claims have not been canceled. Claims 1 – 14 remain pending and have been considered on the merits. All arguments have been fully considered.

Claim Objections

Claim objections have been withdrawn due to amendment.

Claim Rejections - 35 USC § 112

Rejections under 35 U.S.C. 112, second paragraph, have been withdrawn due to amendment.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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2. Claims 1 – 4, 6 and 12 – 14 stand rejected under 35 U.S.C. 102(b) as being anticipated by Allen-Hoffman.

Applicant claims a method for preparing a seeded dermal equivalent, the method comprising providing a dermal equivalent, keratinocytes and culture media having an air interface; culturing the dermal equivalent in the media; lifting the dermal equivalent to the air interface; seeding the dermal equivalent with the keratinocytes to provide a seeded dermal equivalent; and culturing the seeded dermal equivalent at the interface until the keratinocytes stratify. The keratinocytes are selected from primary human keratinocytes, and immortalized keratinocytes, specifically wherein the immortalized keratinocytes are NIKS. The dermal equivalent comprises collagen and fibroblasts and the fibroblasts are NHDF cells. The method further comprises incubating the seeded dermal equivalent such that a skin equivalent is formed, wherein the skin equivalent is stratified into squamous epithelia.

Allen-Hoffmann teaches a method for making a stratified squamous epithelia (abstract) wherein NIKS (see abstract, col.3 line 45-52) cells (immortalized keratinocytes) are seeded onto a base dermal equivalent of collagen and normal human fibroblasts (col.4, line 57-60). The dermal equivalent is lifted to the air interface to provide a lifted dermal equivalent (col.15, line 20-39).

The method anticipates the claimed subject matter.

Applicant argues that the reference teaches re-submerging the seeded dermis, not wherein the seeded equivalent is cultured at the air interface until stratification of the keratinocytes.

However, this argument fails to persuade because Allen-Hoffman clearly teaches culturing the keratinocytes at the air interface until the keratinocytes stratify (col.15 line 20-39). Therefore, the claims remain rejected for this and the reasons above.

3. Claims 1 – 2, 4 – 6 and 12 – 13 stand rejected under 35 U.S.C. 102(b) as being anticipated by Yang.

Applicant claims a method for preparing a seeded dermal equivalent, the method comprising providing a dermal equivalent, keratinocytes and culture media having an air interface; culturing the dermal equivalent in the media; lifting the dermal equivalent to the air interface; seeding the dermal equivalent with the keratinocytes to provided a seeded dermal equivalent; and culturing the seeded dermal equivalent at the interface until the keratinocytes stratify. The keratinocytes are selected from primary human keratinocytes and immortalized keratinocytes, and the dermal equivalent comprises collagen and fibroblasts. Specifically the collagen is rat tail tendon collagen and the fibroblasts are NHDF cells. The lifting step further comprises incubating the lifted dermal equivalent to the air interface for at least 6, 12 or 18 hours before seeding. The method further comprises incubating the seeded dermal equivalent such that a skin equivalent is formed, wherein the skin equivalent is stratified.

Yang teaches a method for making a stratified skin equivalent, wherein the method comprises layering a dermal matrix of fibroblasts and collagen with keratinocytes and culturing the dermal equivalent at the air-liquid interface (abstract). Specifically, rat tail tendon collagen was combined with normal human fibroblasts to create the dermal equivalent which was seeded

with keratinocytes (p.8, collagen and cells). The dermal equivalent was lifted prior to seeding (p.9, preparation of dermal equivalent). The skin was made by seeding keratinocytes onto the dermis, and was further cultured at the air-liquid interface (p.10, production of artificial skin).

The reference anticipated the claimed subject matter.

Applicant argues that Yang re-submerges the seeded culture, and does not keep the seeded keratinocytes at the air interface until stratification.

However, this argument fails to persuade because while Yang does re-submerge the dermal layer after seeding, the seeded layer is brought back to the air interface until stratification of the keratinocytes (abstract, p.10). Therefore, while Yang does contain more steps than the claimed method, it is noted that the claims are not limited to the claimed steps (i.e. by the recitation of "comprising").

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1 – 2 and 4 – 13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Yang.

Applicant claims a method for preparing a seeded dermal equivalent, the method comprising providing a dermal equivalent, keratinocytes and culture media having an air interface; culturing the dermal equivalent in the media; lifting the dermal equivalent to the air interface; seeding the dermal equivalent with the keratinocytes to provided a seeded dermal equivalent; and culturing the seeded dermal equivalent at the interface until the keratinocytes stratify. The keratinocytes are selected from primary human keratinocytes and immortalized keratinocytes, and the dermal equivalent comprises collagen and fibroblasts. Specifically the collagen is rat tail tendon collagen and the fibroblasts are NHDF cells. The lifting step further comprises incubating the lifted dermal equivalent to the air interface for at least 6, 12 or 18 hours before seeding, or for about 24 or 6 – 24 hours. The method further comprises incubating the seeded dermal equivalent such that a skin equivalent is formed, wherein the skin equivalent is stratified.

Yang teaches a method for making a stratified skin equivalent, wherein the method comprises layering a dermal matrix of fibroblasts and collagen with keratinocytes and culturing the dermal equivalent at the air-liquid interface (abstract). Specifically, rat tail tendon collagen

was combined with normal human fibroblasts to create the dermal equivalent which was seeded with keratinocytes (p.8, collagen and cells). The dermal equivalent was lifted prior to seeding (p.9, preparation of dermal equivalent). The skin was made by seeding keratinocytes onto the dermis, and was further cultured at the air-liquid interface (p.10, production of artificial skin).

Yang does not teach the method wherein the incubating lasts for about 24 hours, or 6 – 24 hours. However, at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize incubation times as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by routine practice to optimize the incubation times of Yang with a reasonable expectation for successfully making a stratified skin equivalent.

7. Claims 1 – 4 and 6 – 14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Allen-Hoffman.

Applicant claims a method for preparing a seeded dermal equivalent, the method comprising providing a dermal equivalent, keratinocytes and culture media having an air interface; culturing the dermal equivalent in the media; lifting the dermal equivalent to the air interface; seeding the dermal equivalent with the keratinocytes to provided a seeded dermal equivalent; and culturing the seeded dermal equivalent at the interface until the keratinocytes stratify. The keratinocytes are selected from primary human keratinocytes, and immortalized keratinocytes, specifically wherein the immortalized keratinocytes are NIKS. The dermal equivalent comprises collagen and fibroblasts and the fibroblasts are NHDF cells. The method further comprises incubating the seeded dermal equivalent such that a skin equivalent is formed,

wherein the skin equivalent is stratified into squamous epithelia. The lifting step further comprises incubating the lifted dermal equivalent to the air interface for at least about 6, 12 or 18 hours before seeding, or about 24 or 6 – 24 hours.

Allen-Hoffmann teaches a method for making a stratified squamous epithelia (abstract) wherein NIKS (see abstract, col.3 line 45-52) cells (immortalized keratinocytes) are seeded onto a base dermal equivalent of collagen and normal human fibroblasts (col.4, line 57-60). The dermal equivalent is lifted to the air interface to provide a lifted dermal equivalent (col.15, line 20-39).

Allen-Hoffman does not teach the methods with the claimed incubation times. However, at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize incubation times as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by routine practice to optimize the incubation times of Allen-Hoffmann with a reasonable expectation for successfully making a stratified skin equivalent.

8. Claims 1 – 14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Yang in view of Hoffman.

Applicant claims a method for preparing a seeded dermal equivalent, the method comprising providing a dermal equivalent, keratinocytes and culture media having an air interface; culturing the dermal equivalent in the media; lifting the dermal equivalent to the air interface; seeding the dermal equivalent with the keratinocytes to provided a seeded dermal equivalent; and culturing the seeded dermal equivalent at the interface until the keratinocytes

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stratify. The keratinocytes are selected from primary human keratinocytes, and immortalized keratinocytes, wherein the immortalized keratinocytes are NIKS. The dermal equivalent comprises collagen and fibroblasts, specifically rat tail tendon collagen and NHDF cells. The lifting step further comprises incubating the lifted dermal equivalent to the air interface for at least about 6, 12 or 18 hours before seeding; or alternatively 24 or 6 – 24 hours. The method further comprises incubating the seeded dermal equivalent such that a skin equivalent is formed, wherein the skin equivalent is stratified into squamous epithelia.

Yang teaches a method for making a stratified skin equivalent, wherein the method comprises layering a dermal matrix of fibroblasts and collagen with keratinocytes and culturing the dermal equivalent at the air-liquid interface (abstract). Specifically, rat tail tendon collagen was combined with normal human fibroblasts to create the dermal equivalent which was seeded with keratinocytes (p.8, collagen and cells). The dermal equivalent was lifted prior to seeding (p.9, preparation of dermal equivalent). The skin was made by seeding keratinocytes onto the dermis, and was further cultured at the air-liquid interface (p.10, production of artificial skin).

Yang does not teach the method wherein NIKS cells are used or wherein the stratified skin is squamous epithelia. However, Allen-Hoffmann teaches a method for making a stratified, squamous epithelia (abstract) wherein NIKS (see abstract, col.3 line 45-52) cells (immortalized keratinocytes) are seeded onto a base dermal equivalent of collagen and normal human fibroblasts (col.4, line 57-60). The dermal equivalent is lifted to the air interface to provide a lifted dermal equivalent (col.15, line 20-39). At the time of the claimed invention, one of ordinary skill in the art would have been motivated to use the keratinocytes of Allen-Hoffmann in the methods of Yang because Allen-Hoffmann teaches the cultures are useful in tissue

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engineered products (col.4 line 14-21). In addition, one of ordinary skill in the art would have been motivated to make the stratified skin of Yang into squamous epithelia because it was known to be effective for skin models, as evidenced by Yang and Allen-Hoffmann. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated to use the keratinocytes of Allen-Hoffmann in the methods of Yang with a reasonable expectation for successfully making a dermal/skin equivalent.

The references do not teach the methods with the claimed incubation times. However, at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize incubation times as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by routine practice to optimize the incubation times of Yang and/or Allen-Hoffmann with a reasonable expectation for successfully making a stratified skin equivalent.

Applicant argues that the above references teach re-submerging the cultures after seeding, not wherein the cultures are maintained at the air interface until keratinocyte stratification. Applicant additionally argues that the references do not teach incubating the raised dermal equivalent at the air interface prior to seeding with keratinocytes; and that it would not have been obvious to one of ordinary skill to do so. Finally applicant argues that examiner applies improper hindsight.

However, as previously stated, while the references do re-submerge the dermal layer after seeding, the seeded layer is brought back to the air interface until stratification of the

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keratinocytes. Therefore, while the methods of Yang and Allen-Hoffman contain more steps than the claimed method, it is noted that the claims are not limited to the claimed steps (i.e. by the recitation of "comprising").

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Regarding the incubation of the dermal layer prior to seeding the keratinocytes, it is noted that incubation time periods certainly vary in the tissue culture methods, as evidenced by the cited references. Although they do not specifically address a period of time between lifting the dermal layer and seeding with keratinocytes, it is maintained that such time periods are routinely varied in the art. Furthermore, the step does not appear to be critical to the invention, as the resulting skin substitutes of the claimed method and those of the references are the same. It is further noted that applicant does not indicate the step is critical to impart any substantial benefit or unexpected property to the obtained skin substitute. Therefore, the claims remain rejected for these reasons and those made of record.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruth A. Davis whose telephone number is 703-308-6310. The examiner can normally be reached on M-H (7:00-4:30); alt. F (7:00-3:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 703-308-0196. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

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Effective January 20, 2004, any inquires should be made to Ruth Davis whose telephone number is 571-272-0915. The examiner's supervisor, Michael Wityshyn, can be reached at 571-272-0926.

Ruth A. Davis; rad
January 9, 2004.



LEON B. LANKFORD, JR.
PRIMARY EXAMINER